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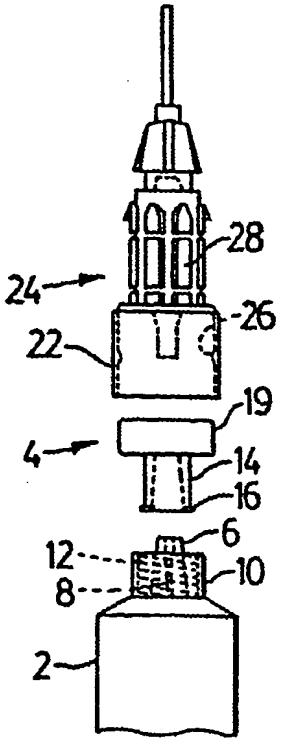
(54) Title: SYRINGE DEVICE FOR ASSEMBLY OF A MULTI-COMPONENT PHARMACEUTICAL



(57) **Abstract:** A syringe is used for assembling components of a pharmaceutical in a delivery system for a multiple component pharmaceutical. The syringe is used in conjunction with an adaptor cap and a transfer mechanism containing a double ended needle assembly to transfer a liquid component between the syringe and at least one other penetrable vessel including a vial containing a further component of the pharmaceutical which is then drawn back with the liquid into the protosyringe. Depending upon the application, the transfer mechanism or part of it may then be removed and discarded, including the vial and at least that end of the needle assembly penetrating the vial, so as to leave the syringe filled with both components and either presenting a needle coupling comprised by part of the needle assembly retained on the protosyringe, or presenting the original needle coupling of the syringe.

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SYRINGE DEVICE FOR ASSEMBLY OF A MULTI-COMPONENT PHARMACEUTICAL

This invention relates to a delivery system for pharmaceutical containing two or more components, at least one of which is a liquid, in which separately stored components are combined immediately prior to use to provide a syringe from which the combined or reconstituted liquid pharmaceutical can be delivered.

One such system is described in published International Patent Application WO97/25015, in which a pharmaceutical vial is connected to a "protosyringe" by a transfer arrangement which enables a liquid (such as sterile water) stored in the protosyringe to be delivered to the vial, for admixture with the contents of the latter and which contents are then drawn back into the protosyringe, whereupon the protosyringe, together with certain elements of the transfer mechanism which convert it into a syringe, is detached from the remainder of the transfer mechanism and is ready for use upon application of a needle or other injection means. It is of course important that sterility be maintained during this procedure, and to this end the transfer arrangement makes use of an axially movable hub which provides a sheathed and detachable needle to penetrate the vial, and a needle, cannula or other instrumentality to broach the protosyringe. The needle is retained in a discarded portion of the transfer mechanism, its detachment leaving a standard needle coupling or luer lock on a portion of the transfer mechanism retained on the protosyringe in order to convert it into a complete syringe. Such a standard needle coupling has a central tapered spigot defining an axial liquid passage, and an outer sleeve provided with an internal thread for engaging flanges of a needle hub and drawing a socket in the hub into fluid-tight engagement with the spigot.

One of the most widely used liquid components in such multiple component pharmaceuticals is sterile water or saline solution, and for economy and simple certification, a

suitable form of prepackaged water is desirable. This may make it desirable in certain cases to utilize not a protosyringe as defined in WO97/25015, but an actual low cost syringe, such as the moulded plastic syringes widely utilized in the pharmaceutical industry. Such a syringe may either be prefilled with water or saline solution, or be filled during activation of the syringe from a source such as a flexible bag such as the MINI-BAG bags from Baxter.

I have found that by the simple addition of a specially designed cap, syringes may not only be converted into protosyringes suitable for use in systems disclosed in WO97/25015, but also that with such a syringe, a simplified transfer arrangement is possible which dispenses with the need for an axially movable hub, but nonetheless retains the advantage that the needle used to establish communication with the vial is retained within the discarded transfer mechanism components, whether the latter are discarded before or after delivery of the pharmaceutical. The syringe may either be empty, contain a liquid component of the pharmaceutical, or a non-liquid component.

According to the invention, there is provided a protosyringe comprising firstly a syringe having at a delivery end a standard needle coupling of the type having a central tapered spigot defining a liquid passage communicating with the interior of the syringe and an outer cylindrical sleeve provided with an internal thread for engaging flanges of a needle hub to draw a socket defined in the hub into fluid tight engagement with the spigot; and secondly a cap engaged with the coupling, the cap comprising a hub for engagement with the sleeve, a penetrable closure drawn onto the spigot by the hub, and a cylindrical collar surrounding the penetrable closure to present a disk-like axial external zone of the closure for penetration by a needle or cannula.

The invention extends to a delivery system for a multiple component pharmaceutical product, comprising a protosyringe

as set forth above; at least one pharmaceutical vial containing a further component of the product, and having a neck end closed by a penetrable closure; and a transfer mechanism comprising a first socket at one end for receiving the cap and delivery end of the protosyringe, a second socket at an opposite end for receiving the closure and neck end of the vial, and a double ended needle assembly for penetrating respectively the penetrable closure of the vial and the cap so as to place the syringe and the vial in communication, such that the first component introduced into the syringe can be transferred to the vial to take up the component stored in the vial and then reaspirated into the syringe.

Preferably, at least a portion of the needle assembly penetrating the penetrable closure of the vial is removed and discarded, retained within a discarded portion of the transfer mechanism. In one embodiment, that portion of the needle assembly which penetrates the vial closure is pulled away from the remainder to leave a standard needle coupling as disclosed in WO97/25015 while, in another embodiment, the cap applied to the prefilled syringe is retained in the transfer mechanism together with the entire needle assembly so as to leave the prefilled syringe containing the combined contents of the syringe and the vial. Even if the reconstituted pharmaceutical is delivered through the transfer mechanism, the needles used for the transfer are safely retained within the mechanism until it is discarded after use.

Further features of the invention will be apparent from the following description with reference to the accompanying drawings, in which:

Figure 1 is an assembled elevational view of a first embodiment of a pharmaceutical delivery system incorporating a protosyringe in accordance with the invention, prior to activation;

Figure 2 is an enlarged detail of certain parts of the system of Figure 1;

Figure 3 is a cross-sectional view of one of the parts shown in Figure 2;

Figure 4 is an elevational view of a second embodiment of a pharmaceutical delivery system incorporating a protosyringe in accordance with the invention, prior to activation;

Figure 5 is an exploded view of parts of the system of Figure 4;

Figures 6, 7, 8, 9 and 10 illustrate successive stages in the deployment of the embodiment of Figure 4 to provide a syringe prefilled with a two-component medicament.

Referring to the drawings, the embodiment shown in Figures 1-3 is similar in most respects to that shown in Figure 21 of WO97/25015, except that the "protosyringe" shown in that embodiment is replaced by the combination of a syringe 2 with a special cap 4 which, in effect, converts it into a protosyringe. Such an arrangement has the advantage that the syringe may be, for example, a mass-produced moulded plastic syringe as shown, incorporating a standard needle coupling or luer lock comprising a conical spigot 6 with a central passage 8 communicating with the syringe body surrounded by cylindrical sleeve 10 with internal threads 12 for coupling with flanges on the hub of a needle.

Instead of a needle, the syringe, usually after being filled with a liquid component of the pharmaceutical, typically but not necessarily sterile water or saline solution, is capped by the cap 4, which, as best seen in Figures 2 and 3, comprises a luer extension 14 with flanges 16 which engages the threads 12, a penetrable rubber disk seal 18, and an annular aluminum collar 19 which clamps the assembly together to produce a cylindrical head with a penetrable seal

comparable to that of the bottomless vials exemplified as protosyringes in WO97/25015. When the assembly is activated, a needle or cannula within a rubber sheath 20 penetrates the seal 18 as the head formed by the cap is forced up into a cap 22 attached to a hub 24 past a detent 26.

Preferably the cap 22 is dimensioned so that, once the head passes the detent 26, it can rotate freely in the cap, thus preventing the syringe 2 from being unscrewed from the cap 4. Alternatively, the ribs 28 shown on the hub could be omitted so that the hub can rotate freely within the transfer assembly 30 (see Figure 1). The transfer assembly comprises screw-connected cylindrical parts 32 and 34, the part 32 defining a socket for the syringe 2, and the part 34 a socket for the neck end and penetrable seal of a vial 36. The penetrable seal of the vial 36 is penetrated by a needle within a sheath 38 as the head formed by the cap 4 is forced into the cap 22 and projects the hub 24 upwardly such that a hub 40 of the needle is gripped by claws 42 formed within cylindrical part 34.

At this point, the needle assembly formed by the hub 24 has established communication between the syringe 2 and the vial 36 so that liquid from the syringe may be projected into the vial to mix with, dissolve or suspend the contents of the latter, the content of the vial then being aspirated back into the syringe. At this point, the part 34 of the transfer assembly may be unscrewed from the part 32, at which point the claws 42 gripping the hub 40 pull the latter off the hub 24, leaving exposed a standard needle coupling (not shown) hitherto covered by the hub 4. The needle that penetrates the vial is thus retained within the portion of the transfer assembly that is discarded with the vial.

It should be understood that the vial 36 may be removed and replaced by a further vial or vials, if additional components are to be introduced into the syringe. Indeed, the syringe 2 may start off empty or containing a non-liquid component of

the pharmaceutical, and initially be filled with liquid from a vial 36, or the socket portion 24 may be engaged with, and pierce a penetrable septum of a nipple of a flexible liquid filled bag such as a Baxter Mini-Bag™, an adaptor being provided, if necessary. In such a case, a further component or components of the pharmaceutical would be admixed by removing the bag and then inserting a vial 36, or multiple vials 36 in succession, after which the bag could if desired be reattached and the contents of the syringe returned to the bag prior to discarding the syringe and transfer assembly.

The structure of the cap 4 may also be varied. The extension 14 may be of plastic or metal, and certain of the parts might possibly be formed integrally, consistent with the function of providing a cylindrical head converting the syringe to a protosyringe, which head provides an external annular surface engageable with the transfer mechanism, and a penetrable seal which will seal hermetically the needle coupling of the syringe.

In the embodiment just described, the cap 4 remains locked to the syringe 2 even after the system is activated, and indeed steps are taken to prevent disengagement of the syringe 2. In a variation, the cap 4 is locked against rotation relative to the transfer mechanism for example by providing longitudinal ribs on the interior of the cap 22, so that, instead of separating the components of the transfer mechanism to complete activation of the system, the syringe 2 is simply unscrewed from the transfer mechanism, the whole of which is then discarded.

Such an arrangement however permits the transfer mechanism to be simplified, as further illustrated with reference to Figures 4-10.

As compared to Figures 1 and 2, the parts 32 and 34 of the transfer assembly are formed in one piece or permanently connected, and the hub 24 and associated parts are omitted

and replaced by a standard needle connection 50 to which is mounted the hub 54 of a double-ended needle 52. The needle may be a conventional steel needle, or moulded from synthetic plastic material. The cap 22 is integral with the part 32 of the transfer assembly instead of the hub 24. The assembly is typically shipped with the head of the protosyringe formed by the syringe 2 and cap 4 (which may be identical to those of the previous embodiment) inserted part way into the cap 22 so that the lower end 56 of the needle 52 does not penetrate the seal. The socket for the vial 36 formed by the part 34 is closed by a flip-off closure 60.

In use, the closure 60 is flipped off, as is any flip-off disc 62 over the penetrable seal of the vial 36 (see Figure 6). The vial 36 is then pushed into its socket (see Figure 7) causing an upper end 64 of the needle 52 to penetrate the closure of the vial and forcing the transfer mechanism down so that the needle end 56 penetrates the seal 18, placing the vial and syringe in communication. The plunger 66 of the vial is used to project liquid from the syringe into the vial to mix with, dissolve or suspend the component of the pharmaceutical contained in the vial (see Figure 8), which is then drawn back into the vial (Figure 9), at which point the syringe 2 is unscrewed from the cap 4, which, together with the needle 52, is retained in the transfer mechanism which is discarded with the vial.

Although the invention has been described with reference to specific embodiments of transfer mechanism, it will be understood that other transfer mechanisms may be used which have sockets for the receipt of vessels, at least one of which is a protosyringe, and which permit transfer of fluids between the vessels after penetrable seals of the vessels have been penetrated by cannulas in the sockets.

CLAIMS

1. A protosyringe comprising firstly a syringe having at a delivery end a standard needle coupling of the type having a central tapered spigot defining a liquid passage communicating with the interior of the syringe and an outer cylindrical sleeve provided with an internal thread for engaging flanges of a needle hub to draw a socket defined in the hub into fluid tight engagement with the spigot; and secondly a cap engaged with the coupling, the cap comprising a hub for engagement with the sleeve, a penetrable closure drawn onto the spigot by the hub, and a cylindrical collar surrounding the penetrable closure to present a disk-like axial external zone of the closure for penetration by a needle or cannula.

2. A syringe according to claim 1, wherein the penetrable closure is of elastomeric material, and the collar is of aluminum, crimped onto the closure and the hub to secure them together.

3. A syringe according to claim 1 or 2, wherein the hub has flanges for engagement with the sleeve.

4. A delivery system for a multiple component pharmaceutical product including a first, liquid component; comprising a protosyringe as claimed in claim 1; at least one pharmaceutical vial containing a further component of the product, and having a neck end closed by a penetrable closure; and a transfer mechanism comprising a first socket at one end for receiving the cap and delivery end of the protosyringe, a second socket at an opposite end for receiving the closure and neck end of the vial, and a double ended needle assembly for penetrating respectively the penetrable closure of the vial and the cap so as to place the syringe and the vial in communication, such that the first component introduced into the syringe can be transferred to the vial to take up the component stored in the vial and then

reaspirated into the syringe.

5. A syringe according to claim 4, wherein removal of at least part of the transfer mechanism from the protosyringe will leave a syringe presenting a standard needle coupling ready to receive a needle or equivalent instrumentality.

6. A delivery system according to claim 5, wherein the at least part of the transfer mechanism which is removable includes at least a portion of the needle assembly for penetrating the closure of the vial.

7. A delivery system according to claims 5 or 6, wherein that portion of the needle assembly for penetrating the vial is a press fit on a standard needle coupling comprised by the remainder of the needle assembly, and is retained by the portion of the transfer mechanism that is removable.

8. A delivery system according to claims 5 or 6, wherein the cap applied to the syringe is retained in the transfer mechanism that is removable.

9. A delivery system according to claim 4, wherein a liquid component of the pharmaceutical is contained in a separate vessel for aspiration into the syringe through the transfer mechanism.

10. A delivery system according to claim 9, wherein the vessel containing the liquid component and the vial containing a further component of the product are sequentially connected to the transfer mechanism.

11. A delivery system according to claim 10, wherein the vessel containing the liquid component is a further vial inserted in the second socket prior to the insertion of the vial containing the second component.

12. A delivery system according to claim 10, wherein the

liquid component is contained in a flexible bag having a nipple with a penetrable septum.

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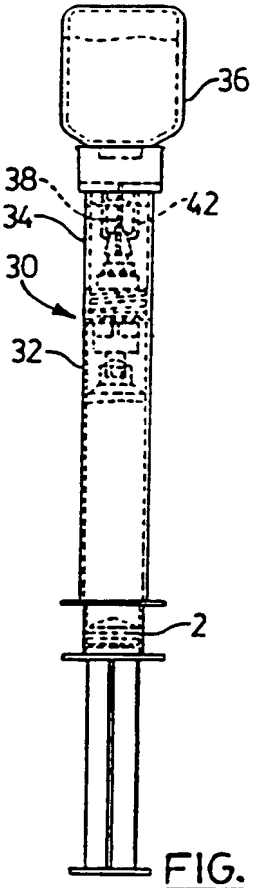

FIG. 1

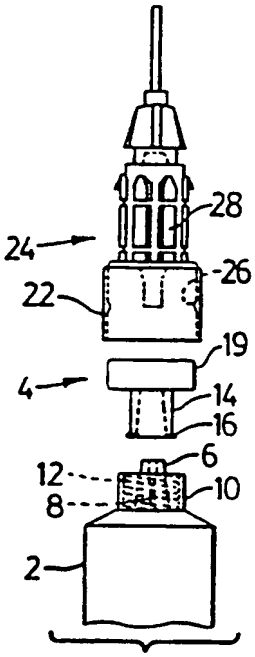

FIG. 2

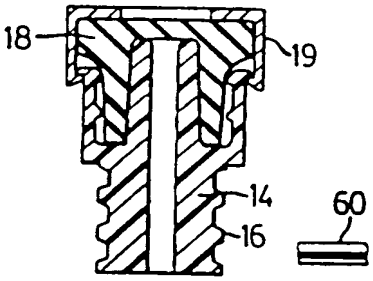

FIG. 3

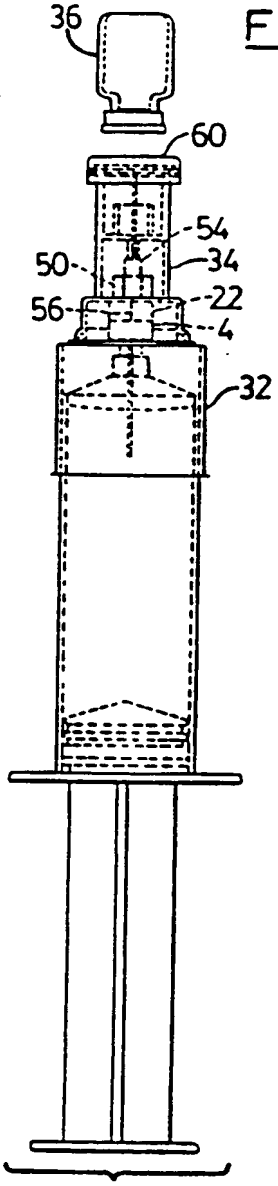

FIG. 4

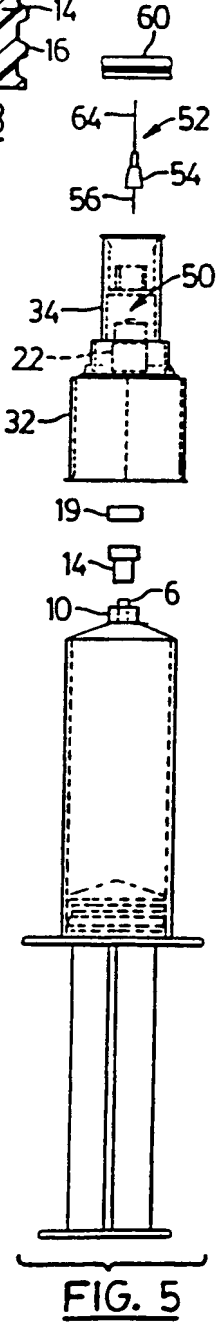

FIG. 5

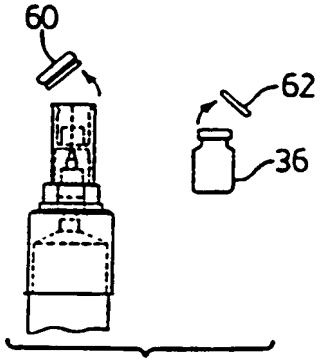

FIG. 6

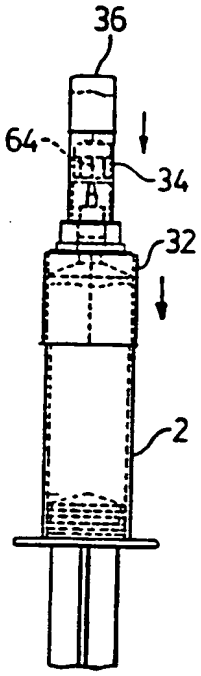

FIG. 7

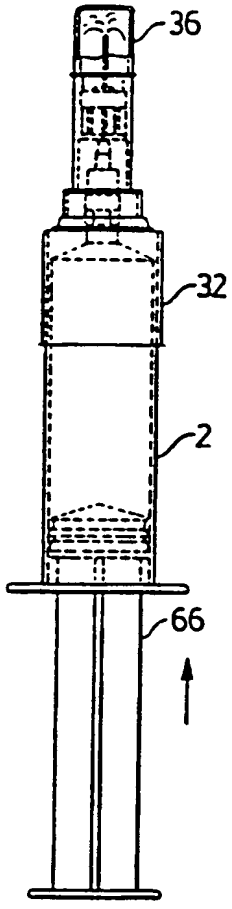

FIG. 8

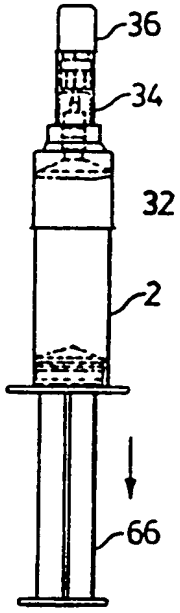

FIG. 9

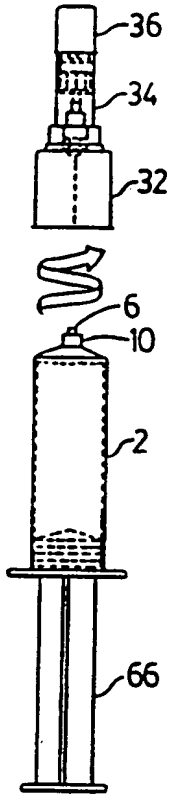

FIG. 10

INTERNATIONAL SEARCH REPORT

Int ional Application No
PCT/CA 00/00699

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 A61J1/00

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 A61J

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal

C. DOCUMENTS CONSIDERED TO BE RELEVANT

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A	page 6, line 5 - line 27; figures	8
Y	EP 0 716 860 A (BECTON DICKINSON CO) 19 June 1996 (1996-06-19) column 7, line 24 - line 35; figure 8	1-7,9-12
A	US 4 898 209 A (ZDEB BRIAN D) 6 February 1990 (1990-02-06) column 8, line 44 - line 55; figures	1-12
P,A	WO 99 27886 A (BAXTER INT) 10 June 1999 (1999-06-10) page 21, line 25 - line 31; figure 11	1-12

☐ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

* Special categories of cited documents :

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Date of the actual completion of the international search	Date of mailing of the international search report
21 September 2000	04/10/2000

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Cametz, C

Form PCT/ISA/210 (second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

Information on patent family members

Int tional Application No
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